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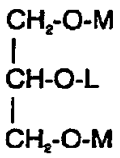
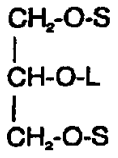
(54) Title: USE OF A LIPID FOR PRODUCTION OF A PHARMACEUTICAL ENTERAL PREPARATION FOR TREATMENT OF LIPID MALABSORPTION



(I)



(II)

(57) Abstract

The lipid is of the type (I) and/or (II) where L is a long chain acyl radical, M is a medium chain acyl radical, and S is a short chain acid radical. This lipid can successfully be used for production of a pharmaceutical preparation for treatment of pancreatic insufficiency, primary biliary cirrhosis or cystic fibrosis.

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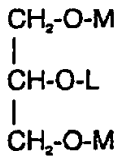
USE OF A LIPID FOR PRODUCTION OF A PHARMACEUTICAL ENTERAL PREPARATION FOR TREATMENT OF LIPID MALABSORPTION

The invention comprises a new use of a lipid of a specified kind.

The lipid in question is of the type MLM and/or SLS. L, which represents a long chain acyl radical, is an acyl radical with 14-24 C atoms, e.g. palmitoyl ($CH_3(CH_2)_{14}CO$-), M, which represents a medium chain acyl radical, is an acyl radical with 6-13 C atoms, e.g. pelargoyl ($CH_3(CH_2)_7CO$-), and S, which represents a short chain acyl radical, is an acyl radical with 2-5 C atoms, e.g. valeroyl ($CH_3(CH_2)_3CO$-). It is understood that a lipid of the type MLM can be represented as



In e.g. WO 90/04009 specific examples of enteral emulsions of lipids of the above indicated type are described, and likewise their use for nutritional purposes. Also, it is described that enteral emulsions of the above indicated type can be used as nutrition for seriously ill patients.

From PCT/DK 90/00343 (not yet published) it appears that lipids of the above indicated kind can be used as an agent with biological effect on the intestinal mucosa.

The purpose of the invention is to provide other uses for lipids of the above indicated type.

Now, surprisingly, it has been found that the lipids of the above indicated type can be used for treatment of patients with lipid malabsorption, e.g. patients suffering from pancreatic insufficiency, primary biliary cirrhosis or cystic fibrosis, i.e. that those lipids can be used for patients suffering from lipid malabsorption. One category of patients with lipid malabsorption has reduced capability in regard to secretion of pancreatic lipase, which is responsible for the major part of triglyceride hydrolysis in the gut.

Thus, surprisingly, according to the invention it has been found that lipids of the type MLM and/or SLS can be absorbed in the gut in spite of reduced or completely absent activity of pancreatic lipase. Structured lipids of the MLM type is easier hydrolyzed by pancreatic lipase (*vide* Example 1), meaning that even at a very low activity of pancreatic lipase, as in patients suffering from pancreatic insufficiency, the structured lipids of the MLM type will be hydrolyzed, and the formed 2-monoglycerides will be absorbed. It appears from Example 2 that feeding MLM to a pancreatic insufficient pig leads to as much lipid absorption as when feeding soy oil to a pancreatic sufficient pig. A study of pancreatic insufficient rats (*vide* Example 3) has shown that the total lipid absorption is greater when provided as structured MLM than as randomized MLM or a physical mixture of the corresponding lipids. In addition the content of the essential fatty acid linoleic acid in the lymph was higher in the MLM group, meaning that the total absorption of linoleic acid was higher. This shows that in addition to providing more easily absorbed energy the MLM also provides essential fatty acids for the functions of the cell, including formation of membrane lipids and intracellular mediators, e.g. eicosanoids. Furthermore, these results indicate that MLM can be absorbed through the gut mucosa without prior hydrolysis.

Thus, the use according to the invention of a lipid of the type MLM and/or SLS is for production of a pharmaceutical preparation for treatment of lipid malabsorption. The lipid related to the use according to the invention can be formulated as a part of a dressing or an oil incorporated in the diet or as a part of an emulsion. Typically the lipid should be administered in an amount of 0.5-4.5 g per kg of body weight per day. The use according to the invention relates to lipid malabsorption in both humans and animals.

Expressed otherwise the use according to the invention of a lipid of the type MLM and/or SLS is for patients suffering from lipid malabsorption.

In a preferred embodiment of the use according to the invention the lipid contains more than 20% of lipids of the type MLM. This type of lipid is easily absorbed in the gut.

In a preferred embodiment of the use according to the invention the lipid contains more than 10% of lipids of the type SLS. This type of lipid is easily absorbed in the gut.

In a preferred embodiment of the use according to the invention the preparation is formulated as an enteral formulation.

Thus, to summarize, lipids of the type MLM or SLS are described, and so are their use as a nutritional agent, and also, use of lipids for treatment of lipid malabsorption are described, but not in relation to lipids of the type MLM or SLS; in particular WO-A-8,902,275 (New England Deaconess Hospital Corp.), WO-A-9,012,080 (New England Deaconess Hospital Corp.), WO-A-8,601,715 (Center for Nutritional Research Charitable Trust), Can. J. Physiol. Pharmacol., vol 68, 1990, pages 519-523, CA; B.P.C. Chow et al.: "Absorption of triglycerides in the absence of lipase", and The American Journal of Clinical Nutrition, vol. 36, November 1982, pages 950-962, American Society for Clinical Nutrition, US; A.C. Bach et al.: "Medium-chain triglycerides: an update" describe different lipids with defined composition and the use of these for treatment of lipid malabsorption, but the lipids used according to the invention are not described in these references.

Lipids for enteral nutrition of the type LLL can only be absorbed with difficulty by patients suffering from lipid malabsorption. Lipids for enteral nutrition of the type MMM, even if they can be absorbed in the mucosa membrane in the absence of pancreatic lipase, do not contain L and thus do not contribute to the formation of essential fatty acids and synthesis of cell membranes in the body, but only to the coverage of the energy demand, as M contributes to the coverage of the energy demand and L contributes to the formation of essential fatty acids and synthesis of cell membranes in the body. The absorption of MMM might be due to a smaller molecular weight and a more compact structure and also a facilitated diffusion across the unstirred water layer of the gut, compared to long chain triglycerides. Reference can be made to Chow, B.P.C., Schaffer, E.A., Parsons, H.G. Absorption of triglycerides in the absence of lipase, Can. J. Physiol. Pharmacol. 68, 519-523, 1990.

However, according to the invention it has been found that the lipids of the above indicated type can be absorbed in individuals suffering from pancreatic insufficiency, thus providing essential fatty acids.

EXAMPLE 1

Hydrolysis of lipids of the MLM type by pancreatic lipase

Experimental:

The hydrolysis of triglycerides in 10% emulsions was measured with pancreatic lipase by pH-stat titration at pH 9 and 37°C. Lipid emulsions (50 ml) were prepared from 5 ml of lipid, 41 ml of gum arabic (10% w/v) and 4 ml of water and emulsified with Ultra Turrax 3 x 5 minutes at 4°C. The particle size distribution was measured microscopically before and after the titrations. For the incubation mixture 2.5 ml of lipid emulsion, 2.0 ml of buffer (0.005 M tris, 0.04 M NaCl) and 0.5 ml of taurocholate solution (8% w/w) were mixed and after equilibration at 37°C the mixture was titrated to an end point of pH 9 with 0.05 N NaOH. 2.0 ml of enzyme solution (25 μg) was added and after 2 minutes of stabilization the rate of base addition was determined at pH 9.

Results:

The titrations were performed under conditions with excess of lipid substrate, and all titration curves turned out to be linear.

As is obvious from Table 1, the introduction of C_8 and/or C_{10} in the 1- and 3-position increases the hydrolysis rate by pancreatic lipase significantly.

Table 1: Hydrolysis rates of different MLM structures

	Lipid	Hydrolysis rate[a] (μmol/-minute/mg of enzyme)	% increase of hydrolysis rate[b]
(prior art)	ARA oil[c]	9.5	
(invention)	C_8/C_{10}-ARA-C_8/C_{10}	20.8	119%
(prior art)	GLA oil[d]	12.0	
(invention)	C_8/C_{10}-GLA-C_8/C_{10}	18.8	57%
(prior art)	Fish oil 1[e]	14.6	
(invention)	C_8/C_{10}-fish oil 1-C_8/C_{10}	18.5	26%
(prior art)	Canola oil	21.8	
(invention)	C_8/C_{10}-Canola-C_8/C_{10}	24.8	14%
(prior art)	Trisun 100	18.8	
(invention)	C_8/C_{10}-Trisun-C_8/C_{10}	21.2	13%
(prior art)	Fish oil 2[f]	10.8	
(invention)	C_8-fish oil 2-C_8	14.1	31%
(invention)	C_{10}-fish oil 2-C_{10}	13.3	23%

a) The hydrolysis rates are calculated from the formula:

$$\frac{\mu l \text{ base/minute} \times \text{normality of the base}}{\text{mg of enzyme}}$$

The determinations were performed in duplicate

Values are corrected for decrease of enzyme activity with time

b) The increase in hydrolysis rate as compared to long chain triglyceride controls
c) Oil rich in arachidonic acid
d) Oil rich in gamma-linolenic acid
e) Fish oil rich in docosahexaenoic acid
f) Fish oil rich in eicosapentaenoic acid

EXAMPLE 2

Pig experiment

The absorption of C_8/C_{10}-soy bean oil-C_8/C_{10} (MLM) in a pig pancreas insufficient by insertion of a catheter into the pancreatic duct has been studied. The study was divided into three periods; in period 1 the pig was pancreas sufficient and received soy bean oil in the feed, in period 2 the pig was made pancreas insufficient and received soy bean oil, and in period 3 the pig was still pancreas insufficient and received C_8/C_{10}-soy bean oil-C_8/C_{10}. All three periods lasted seven days; the last three days the feces were collected and the fat content determined. As can be seen from Fig. 1 the feces fat output after MLM intake was approximately the same as after soy bean oil intake in the pancreas sufficient pig. This means that this structured lipid is more easily absorbed in a pancreatic insufficient pig model than soy bean oil.

EXAMPLE 3

Absorption of C_8/C_{10}-soy bean oil-C_8/C_{10} into the lymph of pancreas insufficient rats

Experimental:

18 Wistar male rats were divided into three groups receiving respectively C_8/C_{10}-soy bean oil-C_8/C_{10} (MLM), randomized MLM or a physical mixture of soy bean oil and MCT oil. The fatty acid composition of the three lipids was approximately the same. The rats were anaestetized with Mebumal and a catheter was inserted into the bile/pancreatic duct to remove all pancreatic secretions and bile. Lymph was collected by introduction of a catheter in ductus thoracicus. The rats were given an intragastric bolus injection of lipid (0.5 g in a taurocholate emulsion, to which was added 5 mM of choline) and lymph collection was initiated immediately thereafter. The lymph was collected with 0.5 hours intervals for the first 4 hours, thereafter with 1 hour intervals for the next 4 hours.

Results:

Fig. 2 shows the total lymphatic output. The absorption peak is seen 5 hours after dosage, which is later than when pancreatic lipase and bile is present. After the peak the absorption of MLM continues at a higher level than the two other lipids. This leads to a higher total absorption of MLM.

The content of the essential fatty acid linoleic acid in the lymph fractions is shown in Fig. 3. The content of linoleic acid is at a significantly higher level in the MLM group than in the two other groups. Correspondingly the total absorption of linoleic acid is higher in the MLM group.

CLAIMS

1. Use of a lipid of the type MLM and/or SLS for production of a pharmaceutical enteral preparation for treatment of lipid malabsorption.

2. Use of a lipid of the type MLM and/or SLS for patients suffering from lipid malabsorption.

3. Use according to Claims 1 - 2, wherein the lipid contains more than 20% of lipids of the type MLM.

4. Use according to Claims 1 - 2, wherein the lipid contains more than 10% of lipids of the type SLS.

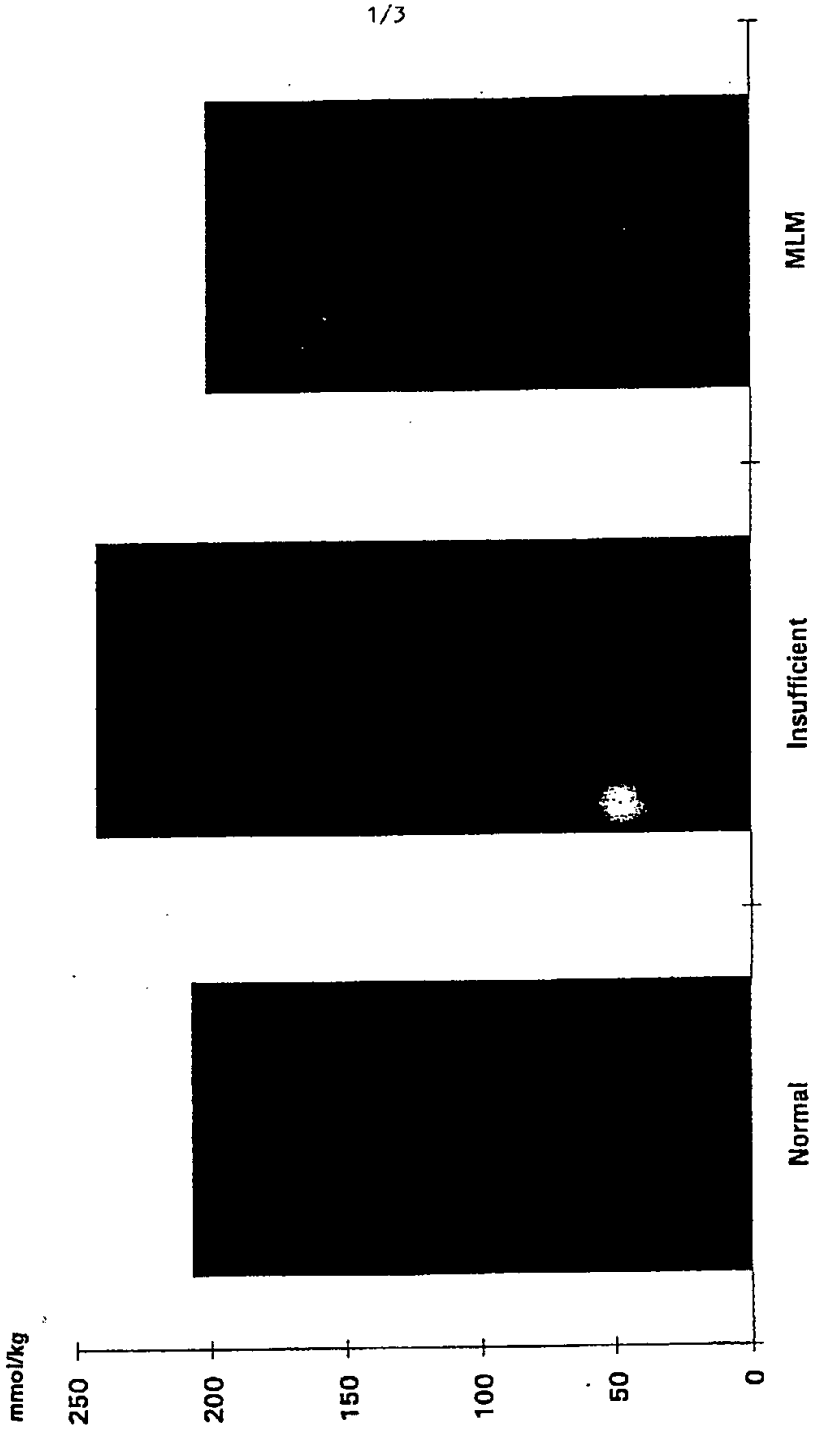


FIG. 1

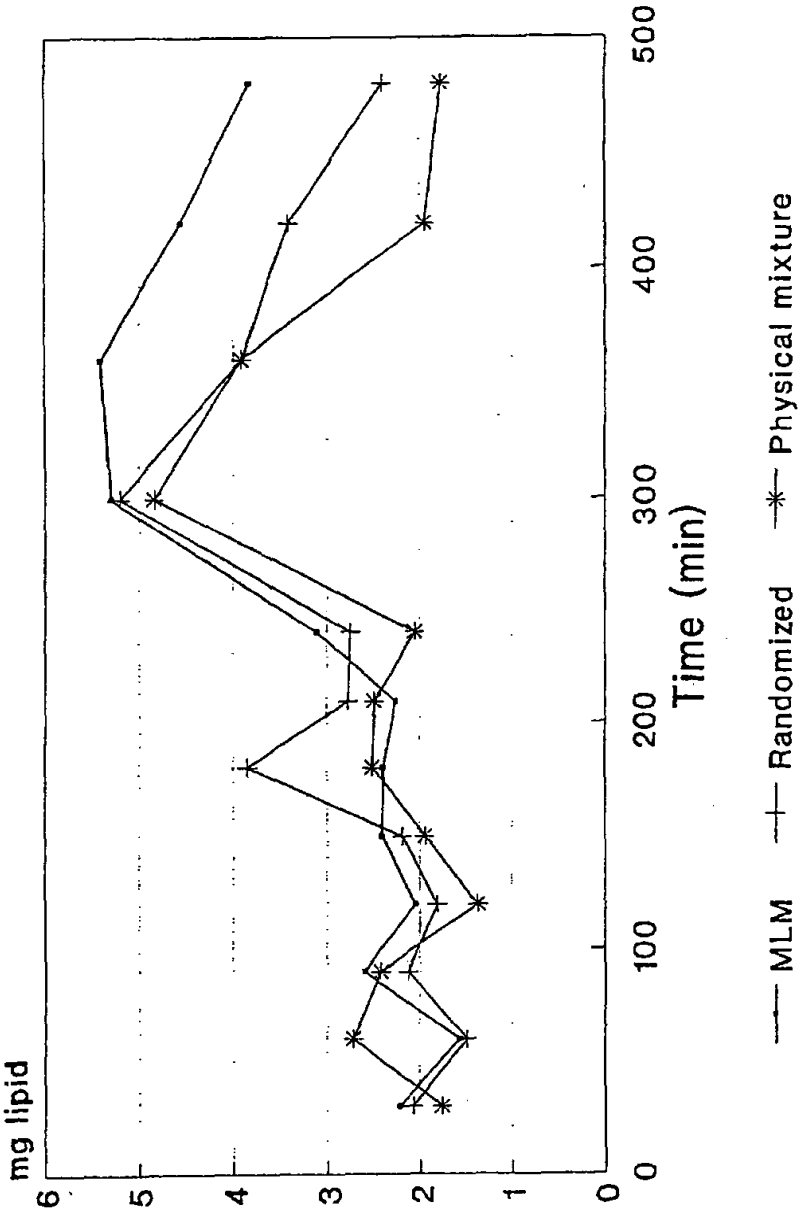

mg lipid
0
1
2
3
4
5
6
0
100
200
300
400
500
Time (min)
MLM
Randomized
Physical mixture

FIG. 2

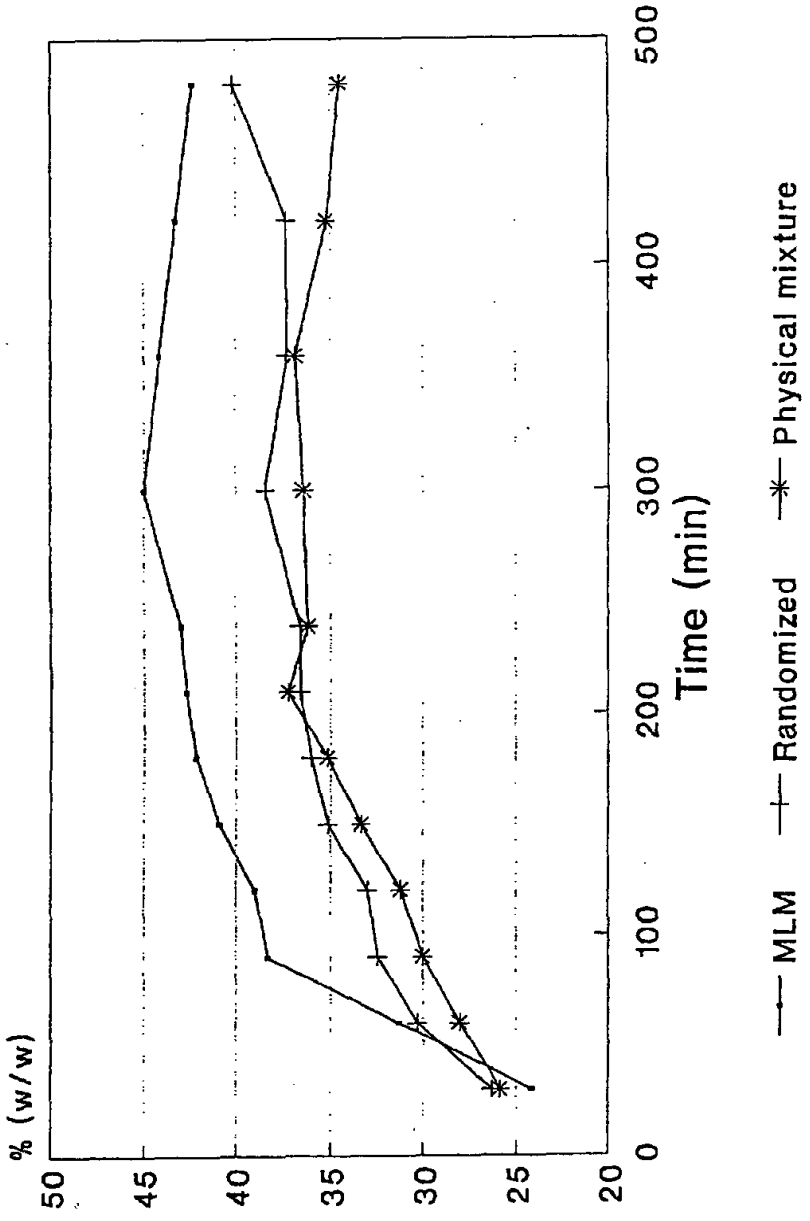

% (w/w)
50
45
40
35
30
25
20
0
100
200
300
400
500
Time (min)
MLM
Randomized
Physical mixture

FIG. 3

INTERNATIONAL SEARCH REPORT

International Application No PCT/DK 92/00150

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 K 31/23

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	A 61 K; C 11 C

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	WO, A1, 9012080 (NEW ENGLAND DEACONESS HOSPITAL CORPORATION) 18 October 1990, see the whole document, particularly page 3 line 25 - page 4 line 4 --	1,3-4
P,X	Dialog Information Services, File 155, Medline 66-90/May, accession no. 07856234, Medline accession no 91375234, Takeda I. et al: "Lymphatic absorption of structured glycerolipids containing medium-chain fatty acids and linoleic acid, and their effect on cholesterol absorption in rats", & Lipids May 1991; 26 (5) p369-73 --	1,3-4
X	Dialog Information Services, File 155, Medline 66-90/May, accession no. 06312169, Medline accession no. 87286169, Rahayan V.K.: "Medium chain triglycerides and structured lipids", & Lipids Jun 1987, 22 (6) p417-20 --	1,3-4

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
24th August 1992	1992 -08- 26
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Gunilla Claesson

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	US, A, 4847296 (VIGEN K. BABAYAN ET AL) 11 July 1989, see the whole document --	1,3-4
X	US, A, 4607052 (FRANCOIS MENDY ET AL) 19 August 1986, see the whole document --	1,3-4
X	US, A, 4528197 (GEORGE L. BLACKBURN) 9 July 1985, see the whole document --	1,3-4

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 2 and 3-4 (partly), because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. ☒ Claim numbers 1, 3-4 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The wording "lipid of the type MLM and/or SLS" is too broadly formulated to permit an adequate search. The search on claims 1, 3-4 has therefore been incomplete. (See PCT, Article 6).

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the the claims. It is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional seach fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.PCT/DK 92/00150

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the Swedish Patent Office EDP file on 31/07/92
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A1- 9012080	90-10-18	AU-D-	5356590	90-11-05
		CA-A-	2051640	90-10-08
		EP-A-	0466768	92-01-22
US-A- 4847296	89-07-11	EP-A-	0193602	86-09-10
		WO-A-	86/01715	86-03-27
US-A- 4607052	86-08-19	US-A-	4701468	87-10-20
		US-A-	4701469	87-10-20
US-A- 4528197	85-07-09	AU-B-	574659	88-07-14
		AU-D-	2378484	84-08-02
		CA-A-	1216188	87-01-06
		EP-A-B-	0121036	84-10-10
		JP-A-	59141522	84-08-14